

BIOGRAPHICAL SKETCH

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NAME: Tumanov, Alexei

eRA COMMONS USER NAME (credential, e.g., agency login): atumanov

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Russian State Medical University, Moscow	M.D.	05/96	Medicine
"Oncoimmunology-Third Millennium" Educational PhD Program in Immunology/Cancer Cell Biology, Cancer Research Institute and Moscow State University	certificate	05/03	Immunology/cancer biology
Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow	Ph.D.	05/03	Immunology/molecular biology
University of Chicago, Department of Pathology	Postdoc/ Res. Assist.Prof.	01/07 07/11	Immunology/pathology

A. Personal Statement

My research focuses on the regulation of mucosal immunity and host response to pathogens. We investigate how the immune system regulates the delicate balance between protective immunity and immunopathology at mucosal surfaces, in particular in the gut. I have extensive training in cytokine biology, immunology, and mouse models of infectious, inflammatory and autoimmune diseases, as well as cancer. The long term goal of my research program is to combine molecular data with *in vivo* models to further the understanding of mechanisms underlying these homeostatic and pathological conditions and aid in the development of cancer therapy. My main research has been centered on understanding the biology of lymphotoxin. I have generated unique cell-type specific lymphotoxin and lymphotoxin beta receptor (LT β R)- deficient mice that will serve as essential models in the proposed study. The ability to specifically manipulate components of the immune response in the mouse allows us to define specific pathways and mechanisms in a way that is not possible with humans. Our recent studies reveal the critical role of LT β R signaling in the regulation of inflammation in the gut by controlling IL-22 production by group 3 innate lymphoid cells (ILCs). A major clinical consequence of inflammatory bowel disease (IBD) is the development of colitis-associated colon cancer, one of the major causes of cancer-related death. My goal for this proposal is to elucidate how LT β R signaling regulates colorectal cancer. This proposal identifies LT β R as a novel cytokine regulator of colorectal cancer and opens a potential for future therapeutic intervention. Collectively, I am convinced that my extensive expertise and experience make me uniquely qualified to bring this research proposal to successful completion.

1. Wang Y., Koroleva E.P., Kruglov A.A., Kuprash D.V., Nedospasov S.A., Fu Y-X, Tumanov A.V. Lymphotoxin beta receptor signaling in intestinal epithelial cells orchestrates innate immune responses against mucosal bacterial infection. **Immunity**, 32(3): 403-13, 2010. PMID: 20226692, PMC: 2878123
2. Chen L., Park S-M., Tumanov A.V., Hau A., Sawada K., Feig C., Turner J.R., Fu Y-X., Romero I., Lengyel E., Peter M.E. CD95/FAS promotes tumor growth. **Nature**, 465(7297):492-6, 2010. PMID: 20505730, PMCID:

PMC2879093

3. Tumanov AV, Koroleva EP, Guo X, Wang Y, Kruglov A, Nedospasov S, Fu YX. Lymphotoxin controls the IL-22 protection pathway in gut innate lymphoid cells during mucosal pathogen challenge. **Cell Host Microbe**, 10(1):44-53, 2011. PMID: 21767811, PMCID: PMC3375029
4. Kruglov A.A., Grivennikov S.I., Kuprash D.V., Winsauer C., Prepens S., Seleznik G. M., Heikenwalder M., Eberl G., Littman D.R., Tumanov A.V., Nedospasov S.A. Non-redundant function of soluble LT α 3 produced by innate lymphoid cells in intestinal homeostasis. **Science**, 342(6163):1243-6, 2013. PMID:24311691

B. Positions and Honors

Positions and Employment

- 1997- 1998 Visiting Scientist, Laboratory of Molecular Immunoregulation, NCI, Frederick, MD, USA
- 1999- 2000 Research Training Fellowship of International Agency for Research on Cancer, Cancer and Developmental Biology Laboratory, NCI, Frederick, MD, USA. Mentor: C. Stewart
- 2000- 2004 Staff Scientist, Laboratory of Molecular Immunology, Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, Moscow, Russia, Mentor: S. Nedospasov
- 2004- 2006 Research Associate (no rank), Department of Pathology, The University of Chicago, Mentor: Yang-Xin Fu
- 2007- 2011 Research Associate (Assistant Professor), Dept of Pathology, The University of Chicago, Mentor: Yang-Xin Fu
- 2011-2016 Assistant Member, Trudeau Institute, Saranac Lake, NY
- 2012-2016 Adjunct Assistant Professor, University of Vermont College of Medicine, Burlington, VT
- 2015-2016 Adjunct Assistant Professor, Clarkson University, NY
- Sep 2016-Present Associate Professor, Department of Microbiology, Immunology, and Molecular Genetics, University of Texas School of Medicine, Health Science Center at San Antonio

Awards

- 1999 Research Training Fellowship of International Agency for Research on Cancer, #R.2903
- 2001 Outstanding Scholar Award. International Cytokine Society
- 2002 International Union Against Cancer (IUCC), IUCC Cancer Technology Transfer Fellowship
- 2003, 2004. Young Scientist Award. Engelhardt Institute of Molecular Biology, Moscow, Russia
- 2003-2004 Grant from Russian Foundation for Basic Research, Ref No:03-04-49097a
- 2007 AAI and Keystone Conference Junior Faculty Travel Awards
- 2007-2009 Scientist Development Grant. American Heart Association, #0730419Z
- 2008, 2009 Pilot and Feasibility Award. University of Chicago Digestive Diseases Research Center, #DK42086
- 2010 Career Development Award. Crohn's and Colitis Foundation of America
- 2012 CCFA Shanthi Sitaraman Memorial Young IBD Investigator Award
- 2013 Junior Faculty Travel Award. 14th International TNF conference
- 2013 Vermont Immunobiology/Infectious Diseases Center Pilot Award
- 2014 Biomedical Research Grant. American Lung Association
- 2014 Senior Research Award. Crohn's and Colitis Foundation of America
- 2015 Clarkson University/Trudeau Institute Partnership (CUTIP) Award

C. Contribution to Science

1. Lymphotoxin-dependent control of innate lymphoid cells.

I became interested in biology of innate lymphoid cells (ILCs) during my work at University of Chicago, and later at Trudeau Institute. We discovered that lymphotoxin beta receptor (LT β R) signaling is critical for the regulation of mucosal immune responses in the gut by controlling the effector functions of innate lymphoid cells (ILCs). We identified LT as a novel driver of IL-22 production by group 3 ILCs. We also discovered the novel role of soluble

LT provided by ILCs for IgA production in the gut and regulation of commensal microbiota. This opens new directions for targeting LT pathway to control mucosal immune responses in the gut.

- a. Wang Y., Koroleva E.P., Kruglov A.A., Kuprash D.V., Nedospasov S.A., Fu Y-X, Tumanov A.V. Lymphotoxin beta receptor signaling in intestinal epithelial cells orchestrates innate immune responses against mucosal bacterial infection. **Immunity**, 32(3): 403-13, 2010. PMID: 20226692, PMC: 2878123
- b. Tumanov AV, Koroleva EP, Guo X, Wang Y, Kruglov A, Nedospasov S, Fu YX. Lymphotoxin controls the IL-22 protection pathway in gut innate lymphoid cells during mucosal pathogen challenge. **Cell Host Microbe**, 10(1):44-53, 2011. PMID: 21767811, PMC3375029
- c. Upadhyay V., Poroyko V., Kim T.J., Devkota S., Fu S., Liu D., Tumanov A.V., Koroleva E.P., Deng L., Nagler C., E. B. Chang, H. Tang, Y. X. Fu. Lymphotoxin regulates commensal responses to enable diet-induced obesity. **Nat Immunol.**, 13(10): 947-53, 2012.
- d. Kruglov A.A., Grivennikov S.I., Kuprash D.V., Winsauer C., Prepens S., Seleznik G. M., Heikenwalder M., Eberl G., Littman D.R., Tumanov A.V., Nedospasov S.A. Non-redundant function of soluble LT α 3 produced by innate lymphoid cells in intestinal homeostasis. **Science**, 342(6163):1243-6, 2013.

2. Regulation of inflammation in the gut.

My work at the Trudeau Institute and currently at the UT Health Science Center at San Antonio is focused on the regulation of inflammatory responses in the gut. We investigate how LT and TNF cytokines regulate inflammatory and protective responses in the gut using several mouse models including *Citrobacter rodentium*, chemically induced colitis and intestinal ischemia-reperfusion induced injury.

- a. Macho-Fernandez E., Koroleva E.P., Spencer C.M., Tighe M., Torrado E., Cooper A.M, Fu Y-X, Tumanov A.V. Lymphotoxin beta receptor signaling limits mucosal damage through driving IL-23 production by epithelial cells. **Mucosal Immunol**, 2015 Mar;8(2):403-13. PMID: 25183367, PMC4364000
- b. Koroleva E.P., Halperin S., Gubernatorova E.O., Spencer C.M, Tumanov A.V. Citrobacter rodentium- induced colitis: a robust model to study mucosal immune responses in the gut. **J Immunol Methods**, 2015, 421:61-72. PMID: 25702536
- c. Gubernatorova E.O., Koroleva E.P., Halperin S., Perez-Chanona E., Jobin C., Tumanov A.V. Murine model of intestinal ischemia-reperfusion injury. **J Vis Exp**, e53881, doi:10.3791/53881, 2016. PMID: 27213580
- d. Gubernatorova E.O. Tumanov A.V. Tumor necrosis factor and lymphotoxin in regulation of intestinal inflammation. **Biochemistry** (Mosc). 81 (11), 2016.

2. Immune regulation of cancer.

With a team of collaborators, we have shown that immune cells (T/NKT) and cytokines (Fas, LIGHT, LT) regulate tumor growth in several mouse models of cancer, in particular, liver cancer and solid tumors. We have shown that LT β R-dependent pathway is critical for control of liver cancer. Therefore, therapeutic manipulation of LT β R pathway opens a novel approach for cancer immunotherapy.

- a. Chen L., Park S-M., Tumanov A.V., Hau A., Sawada K., Feig C., Turner J.R., Fu Y-X., Romero I., Lengyel E., Peter M.E. CD95/FAS promotes tumor growth. **Nature**, 465(7297):492-6, 2010. PMID: 20505730, PMCID: PMC2879093
- b. Daller B, Müsch W, Röhl J, Tumanov AV, Nedospasov SA, Männel DN, Schneider-Brachert W, Hehlhans T. Lymphotoxin- β receptor activation by lymphotoxin- α (1) β (2) and LIGHT promotes tumor growth in an NF κ B-dependent manner. **Int J Cancer**, 128(6):1363-70, 2011. PMID: 20473944
- c. Wolf M.J., Adili A., Piotrowitz K., Abdullah Z., Boege Y., Stemmer K., Ringelhan M., Simonavicius N., Egger M., Wohlleber D., Lorentzen A., Einer C., Schulz S., Clavel T., Protzer U., Thiele C., Zischka H., Moch H., Tschöp M., Tumanov A.V., Haller D., Unger K., Karin M., Kopf M., Knolle P., Weber A., Heikenwalder M. Metabolic activation of intrahepatic CD8(+) T Cells and NKT cells causes nonalcoholic steatohepatitis and liver cancer via cross-talk with hepatocytes. **Cancer Cell**, Oct 13;26(4):549-64, 2014. PMID: 25314080

4. Immune control of liver homeostasis.

My postdoctoral work at the University of Chicago (Mentor: Dr. Yang-Xin Fu) was focused on the role of immune system in the regulation of liver homeostasis. We discovered that innate and adaptive immune cells are actively involved in the regulation of vital functions of the liver, by promoting lipid metabolism and hepatocyte proliferation.

- a. Lo J.C.*, Wang Y.*, Tumanov A.V.*, Bamji M., Yao Z., Reardon C.A., Getz G.S., Fu Y-X. Lymphotoxin beta receptor-dependent control of lipid homeostasis. **Science**, 316(5822):285-8, 2007. PMID:17431181, *Contribute equally
- b. Tumanov A.V., Koroleva E.P., Christiansen P.A., Khan M.A., Ruddy M.J., Burnette B., Papa S., Franzoso G., Nedospasov S., Fu Y-X., Anders R.A. T cell derived lymphotoxin regulates liver regeneration. **Gastroenterology**, 136(2):694-704, 2009. PMID:18952083, PMCID:PMC 3060763
- c. Tumanov A.V., Christiansen P.A., Fu Y-X. The role of lymphotoxin receptor signaling in diseases. **Current Mol. Medicine**, 7: 567-578, 2007. PMID: 17896993

5. Role of LT/TNF cytokines in homeostasis of lymphoid organs and host defense.

After my graduation from the Russian State Medical University in 1996, I joined the Laboratory of Molecular Immunology at the Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (Mentor: Dr. Nedospasov). The main goal of my PhD. thesis was to define the role of lymphotoxin (LT), member of TNF family of cytokines, produced by distinct immune cells, in particular T and B lymphocytes, in the organization of secondary lymphoid organs, using a cell-specific gene targeting approach. We identified distinct mechanisms for LT produced by specific cell types in the organization of secondary lymphoid organs. During these years I acquired extensive knowledge and experience in the LT/TNF field and in conditional gene targeting strategies and have begun to apply this technique in appropriate mouse models to study human infectious diseases and cancer.

- a. Tumanov, A. V., Kuprash, D. V., Grivennikov, S. I., Lagarkova, M. A., Abe, K., Shakhov, A. N., Drutskaya, L. N., Stewart, C. L., Chervonsky, A. V., and Nedospasov, S. A.: Distinct role of surface lymphotoxin expressed by B cells in the organization of secondary lymphoid tissues. **Immunity**. 17: 239-250, 2002. PMID:12354378
- b. Grivennikov, S.I. *, Tumanov, A.V.*, Liepinsh, D. J., Kruglov, A.A., Marakusha, B.I., Shakhov, A.N., Murakami, T., Drutskaya, L.N., Förster, I., Clausen, B.E., Tassarollo, L., Ryffel, Bernhard, Kuprash, D.V., Nedospasov, S.A.: Distinct and non-redundant in vivo functions of TNF produced by T cells and macrophages/neutrophils: protective and deleterious effects. **Immunity**, 22 (1): 93-104, 2005. PMID:15664162 *Contribute equally
- c. Moseman E. A., Iannacone M., Bosurgi L., Tonti E., Chevrier N., Tumanov A., Fu Y-X, N. Hacohen, von Andrian, U.H. 2012. B cell maintenance of subcapsular sinus macrophages protects against a fatal viral infection independent of adaptive Immunity. **Immunity**, 36(3):415-26, 2012. PMID: 22386268, PMC3359130
- d. Koroleva E.P., Fu Y.X., Tumanov A.V. Lymphotoxin in physiology of lymphoid tissues - Implication for antiviral defense. **Cytokine**. Sep 9. pii: S1043-4666(16)30472-0, 2016.

Complete List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/alexei.tumanov.1/bibliography/51517916/public/?sort=date&direction=ascending>

D. Research Support

Ongoing Research Support

Senior Research Award #294083 (Tumanov) 01/01/14-06/30/17

Crohn's and Colitis Foundation of America

Title: Lymphotoxin-dependent control of colon inflammation

The major goal of this proposal is to investigate the role of Lymphotoxin (LT) in inflammatory bowel disease.

Role: PI

NIH 1R21AI111000-01A1 (Tumanov) 02/01/2015 – 06/30/2017

Title: Defining the role of lymphotoxin signaling in viral-induced lung immunopathology

The major goal of this project is to investigate the role of lymphotoxin signaling in regulation of lung damage during influenza infection. Role: PI

University of Texas Health Science Center at San Antonio startup funds (Tumanov) 09/01/16-09/2019

The major goal of these funds is to generate preliminary data for competitive grant applications

Completed Research Support

RG-310669 (Tumanov)

07/01/14-06/30/16

American Lung Association

Title: Targeting lymphotoxin-beta receptor to inhibit viral-induced lung damage

The major goal of this project is to develop a novel immunotherapeutic approach to inhibit viral-induced lung damage. Role: PI

#CUTIP1EK (Tumanov, Andreescu)

07/01/14-02/01/15

Clarkson University/Trudeau Institute Partnership Award

Title: Nanotherapeutic probes for early detection and therapy of inflammatory diseases

The major goal of this pilot project is to develop a novel immunoengineering approach using electrochemistry-based electrodes for detection of reactive oxygen species and nitric oxide in the intestine as early markers of inflammation. The preliminary data generated during work on this pilot project will be used for larger competitive grant applications.

Role: Co-PI

Career Development Award #2672 (Tumanov)

01/01/10-01/01/13

Crohn's and Colitis Foundation of America

Title: Lymphotoxin beta receptor dependent control of mucosal immune homeostasis

The major role of this proposal is to investigate how lymphotoxin beta receptor signaling controls colon inflammation and protection against mucosal pathogens.

Role: PI

Scientist Development Grant. #0730419Z (Tumanov)

01/01/2007- 01/01/2010

American Heart Association

Title: Regulation of Lipid Metabolism by Lymphotoxin beta Receptor Signaling.

The major goal of this proposal is to define the cellular basis for LIGHT-LT β R signaling on lipid metabolism.

Role: PI

Alexei Tumanov, M.D., Ph.D. Associate Professor, Department of Microbiology, Immunology, Molecular Genetics, UT Health Science Center at San Antonio

Potential projects for Xiangya Medical Students. We are interested in hosting two Xiangya students in the lab.

Project 1. Targeting novel cytokine pathways in colon cancer.

Colorectal cancer (CRC) is the major cause of cancer-related deaths. CRC is a major fatal complication for patients with inflammatory bowel disease. The risk of developing colorectal cancer in patients with inflammatory bowel disease is approximately five times higher than in the general population. Although the link between inflammation and cancer promotion is well established, the cellular and molecular pathways involved remain poorly understood. This gap of knowledge severely limits the development of novel therapies to treat the disease. The long-term goal of this program is to understand the fundamental mechanisms of immune regulation of CRC and apply this knowledge to the development of new immunotherapeutic approaches for treatment of cancer. Our preliminary results suggest that lymphotoxin beta receptor (LT β R), a member of the tumor necrosis factor receptor (TNFR) cytokine superfamily, inhibits the development of colitis-associated cancer and sporadic CRC in well-established mouse models. Recent studies reveal the cytokine interleukin (IL)-22 and its natural soluble inhibitor, IL-22 binding protein (IL-22BP), as critical regulators of CRC. Intriguingly, our preliminary data suggest that LT β R signaling regulates IL-22 cytokine pathway. Thus, the overall objective of this proposal is to elucidate how LT β R signaling inhibits development of CRC. Our working hypothesis is that LT β R signaling inhibits CRC development by activating the IL22-BP inhibitor, and that therapeutic activation of LT β R signaling will inhibit development of colon cancer. To test this hypothesis, we will investigate how LT β R signaling regulate IL-22 cytokine pathway in mouse models and human CRC, and test whether stimulation of LT β R signaling with an agonistic antibody represents a novel therapeutic approach to inhibit colitis-associated cancer and sporadic CRC. Successful completion of this project will define the key LT β R-dependent mechanisms that contribute to CRC, and reveal the potential of LT β R-targeted therapies in treating or preventing it.

Project 2. Overcoming roadblocks of anti-CD137 cancer therapy using LT β R cytokine inhibitor.

Antibody-based strategies for cancer treatment have dramatically advanced during recent years. However, accompanying immune-mediated side effects remain the major obstacle of these therapies. Costimulatory molecule CD137 (4-1BB), a member of TNFR family of cytokines, represents an attractive target for immunotherapy. The efficiency of agonistic anti-CD137 treatment have been demonstrated in various cancers in animal models, by promoting survival and effector functions of CD8⁺T cells. Combination of anti-CD137 agonistic antibody treatment with checkpoint inhibitors such as PD-1 and CTLA-4, further improved the potency of anti-CD137 agonistic treatment. Unfortunately, clinical trials of anti-CD137 agonistic antibody in patients with advanced cancer revealed dramatic liver toxicity which prevented further clinical use of anti-CD137 therapy. Therefore, overcoming liver toxicity of anti-CD137 agonistic antibody treatment is crucial for implementation of anti-CD137-based cancer therapies. Our exciting preliminary studies reveal that inhibition of LT β R, another member of TNFR cytokine family, prevents liver toxicity and liver cancer in mice. Therefore, the objective of this proposal is to test the efficiency of LT β R inhibitors for preventing liver toxicity and improving anti-CD137 cancer therapy. Our working hypothesis is that inhibition of LT β R signaling prevents anti-CD137-mediated liver toxicity thereby improving antitumor therapy. Therefore, we will test whether genetic or biochemical inactivation of LT β R signaling promotes the efficacy of anti-CD137 cancer therapy using mouse models of inflammation-induced liver cancer and transplantable solid tumors.